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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,884	04/07/1999	HAROLD J. WANEBO	58463/JPW/EM	6824

7590 06/06/2007

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/287,884	WANEBO ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 20-41 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 3/16/2007 has been received and entered into the application. Accordingly, claims 20-23, 25, 28 and 30-31 have been amended and claims 34-41 have been added.

In view of the above amendments, the rejection of the claims under 35 U.S.C. 112, 2nd Paragraph has been overcome and thus is *withdrawn*. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement Rejection.

In the instant case, claims 20, 25, and 31 were amended to include the limitation wherein the amount of paclitaxel and C_6-ceramide are effective to induce a 50% death rate of the tumor cells. Thus, the claims are limited to a specific amount of paclitaxel and a specific amount of C_6-ceramide that, when combined, lead to exactly 50% of tumor cell death. It would take undue

experimentation to practice the present invention given the guidance and direction provided in the specification. The present claims require each and every amount of paclitaxel and C6-ceramide to be tested in each individual cancer cell lines to determine which specific doses are effective to induce a 50% death rate. There is no possible way to predict what doses of active agents will achieve this effect. It is noted that in all of the experiments conducted by Applicants, there were no doses of paclitaxel and C_6-ceramide that induced exactly a 50% death rate.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 20, 25, 30-31 and 34-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jayadev *et al.* (J. Biol. Chem., 1995, vol. 270, pages 2047-2052) (prior art of record) in view of Mycek *et al.* (Lippincott's Illustrated Review: Pharmacology 2nd Edition, 1997, pages 376 and 390-392) (prior art of record).

The central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner believes that a *prima facie* case of obvious has been established. Applicants disagree and traverse the present rejection. Applicants' arguments have been fully considered but they fail to persuade the Examiner of error in his determination of obviousness.

Firstly, Applicants argue that a *prima facie* case of obviousness does not exist by asserting that there is no motivation to combine the cited references to create the invention set forth in the presently rejected claims. The Examiner respectfully disagrees. Jayadev *et al.* teach that C_6-ceramide causes apoptosis in Molt-4 leukemia cells through significant G_0/G_1 arrest and Mycek *et al.* teach that paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer and has shown further favorable results in small-cell lung cancer, squamous-cell carcinoma of the head and neck, and "several other cancers". Jayadev *et al.* also teaches that the effects of C_6-ceramide on cell cycle arrest are a generalized phenomenon, not restricted to the Molt-4 cell line (page 2049). In addition, Mycek *et al.* teach that combination therapy of paclitaxel with other anticancer drugs is being evaluated. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer C_6-ceramide in combination with paclitaxel as taught by Jayadev *et al.* in view of the teachings of Mycek *et al.* One would have been motivated to do so because each of the therapeutics have been individually taught in the prior art to be successful at treating cancer, and further, Mycek *et al.* motivates combination therapy for the treatment of cancer using paclitaxel and a second therapeutic agent. Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ

1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering C_6-ceramide in combination with paclitaxel as taught in Jayadev *et al.* in view of the teachings of Mycek *et al.*, one would achieve a method of treating cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In fact, Applicants recognize this motivation to combine wherein they state that paclitaxel combined with other chemotherapeutic agents in the treatment of a variety of cancers, including leukemia, typically produces a stronger tumor cell growth inhibition than a single chemotherapeutic agent (page 2, lines 21-26 of specification).

Applicants have further argued that they have demonstrated unexpected results with respect to the combination of C_6-ceramide and paclitaxel. For example, Applicants argue that the synergism observed when C_6-ceramide is administered in combination with paclitaxel is unexpected. This argument has been duly considered but is not persuasive. There are three *expected* effects that may arise from combination therapy: 1) an additive effect; 2) a synergistic effect; and 3) antagonism. For example, if Compound A and Compound B each increase life expectancy by 1 month when administered as single agents, the skilled artisan would expect that

a combination of Compound A and Compound B would: 1) increase life expectancy by 2 months (additive); 2) increase life expectancy by *more* than 2 months (synergistic); or 3) decrease life expectancy (*less* than 1 month) (antagonism). The fact that Applicants have shown that a combination of C_6-ceramide and paclitaxel is synergistic only demonstrates an expected result. Similarly, if Applicants had shown an additive effect, this too would have been expected. By asserting that a synergistic result is "unexpected", Applicants are implying that only an additive or antagonist effect would be expected. This is simply not the case. The prior art is replete with examples of known anticancer agents being combined to treat cancer. In the majority of cases, such combinations are more effective than single agent therapy. As such, combining two drugs that have both been shown to have anticancer activity, and act through different mechanisms, would have been *prima facie* obvious at the time of the invention.

Accordingly, the claims are deemed properly rejected under 35 U.S.C. § 103 as being obvious over Jayadev *et al.* in view of Mycek *et al.* Applicant's demonstration of synergism is not indicative of an "unexpected" result in the art of chemotherapy.

Claims 20-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spencer *et al.* (Drugs, 1994, vol. 48, pages 794-847) (prior art of record) in view of Cai *et al.* (J. Biol. Chem., 1997, vol. 272, pages 6918-6926) (prior art of record).

As discussed *supra*, the central issue remaining in the present case is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer. The Examiner believes that a *prima facie* case of obvious has been established. Applicants disagree and traverse the present rejection. Applicants' arguments have

been fully considered but they fail to persuade the Examiner of error in his determination of obviousness. Applicant's arguments with respect to the present rejection mirror those presented above. Accordingly, Examiner refers to his response *supra*. Spencer *et al.* teach that paclitaxel has demonstrated broad-spectrum anticancer activity (Table 1). The reference also teaches combination therapy comprising paclitaxel and several other anticancer agents, including cisplatin, cyclophosphamide, doxorubicin, hydroxyurea and dexamethasone (pages 798-799, 805-806 and 821-826). Such combinations are often synergistic as discussed *supra*. Cai *et al.* teach that C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells (pages 6922-6923; Figure 5). As discussed *supra*, while the skilled artisan cannot, *a priori*, predict whether a given combination of drugs will have an additive, synergistic, or antagonistic effect, the skilled artisan would reasonably expect that two anticancer agents would, when combined, be effective to treat cancer. As such, it is, even in the absence of any explicit teachings, *prima facie* obvious to combine two agents known to treat cancer. With respect to Applicants' arguments regarding unexpected results, the courts have recognized that synergism is not, *a priori*, unexpected. "Synergism is one factor to be considered in the ultimate determination of obviousness of the composition . . . we attribute no magic status to synergism per se since it may be expected or unexpected." *In re Huellmantel*, 324 F.2d 998, 1003, 139 USPQ 496, 500 (CCPA 1963). In the instant case of combining two drugs with different mechanisms of action, synergism is one of three *expected* outcomes, the other two being an additive or antagonistic effect. The skilled artisan in the art of chemotherapy would attribute no magical status to synergism because such an effect is often seen in combination chemotherapy.

Accordingly, the claims are deemed properly rejected as being obvious over Spencer *et al.* in view of Cai *et al.* The skilled artisan would have been imbued with at least a reasonable expectation that a combination of paclitaxel and C_6-ceramide would be effective in treating cancer and would further expect that the combination might be synergistic.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

May 31, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

6/1/07